

**REMARKS/ARGUMENTS**

Claims 1, 3-5, 8, 10, 46, and 47 have been revised to utilize the phrase “consisting of” in place of “comprising”. Claims 1, 8, and 46 have also been revised to state that the peptides bind  $\alpha 3\beta 1$  integrin, which is supported by the instant application at least on page 11, lines 27-30. These revisions are not made in acquiescence of any rejection of record but rather is made to better the claims in light of currently contemplated clinical embodiments of the invention. Accordingly, the revision is made for reasons related to commercial and business considerations rather than any issue of patentability.

Claim 46 has also been revised to introduce the appropriate Sequence Identifier without altering the scope of the claim.

Claims 2 and 9 have been revised to clarify the intended scope wherein the tetrameric sequence is present in the peptides of the claims. The scope of claims 2 and 9 have not been changed because they necessarily had all the limitations of claims 1 and 8, from which claims 2 and 9 depend, respectively.

Claim 7 has been revised to be consistent with revised claim 1.

Claims 11, 12, and 15-19 have been canceled as being directed to non-elected inventions. Applicants reserve the right to re-present them in a divisional or other continuing application without prejudice.

Claims 20-45 remain pending because they are subject to rejoinder as discussed below.

New claims 48-52, all dependent from claim 46, have been introduced. These claims correspond to claims 2, 3, 7, 13, and 14 and reflect claimed subject matter when the content of claim 46 was previously present in claim 1. Applicants respectfully submit that these new claims require no additional consideration and ask that they be considered and allowed along with claim 46.

No new matter has been introduced, and entry of the amendments is respectfully requested.

Telephonic Interview of November 17, 2004

Applicants express their thanks for the courtesy of a telephonic interview between Examiners M. Haddad and C. Chan as well as M. Bahar of the NIH (party at interest) and the undersigned. Applicants wish to express their appreciation for the indication that the “new matter” rejection will be withdrawn.

The interview included discussion of all examined claims and cited references from the last Office Action. Applicants’ representatives indicated their willingness to consider revising claims to utilize “consisting of” as the transitional phrase and to state that the peptides bind  $\alpha 3\beta 1$  integrin. The Examiners indicated that such amendments would likely obviate both the rejections based upon cited references as well as rejections under 35 U.S.C. § 112.

Rejoinder

Claims 20-30 and 37-45 remain directed to methods comprising the use of a peptide according to claim 1 (claims 20-29 and 37-45) or claim 2 (claim 30). As such, they have all the limitations of elected claims 1 and 2 and are subject to rejoinder as set forth at MPEP 821.04. Applicants respectfully ask that claims 20-30 and 37-45 be rejoined and allowed along with claims 1 and 2.

Claim Objections

Claim 46 was objected to under 37 CFR 1.821(d) because it lacks a sequence identifier. Applicants respectfully request withdrawal of this objection in light of the amendment to claim 46.

Claim Rejection under 35 U.S.C. § 112, second paragraph

Claims 2 and 9 were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for reciting “from about 4 to about 12 amino acids” because “[i]t is unclear how many amino acids constitute ‘about’”.

Applicants respectfully, but strongly, traverse the instant rejection as failing to present a *prima facie* case of indefiniteness for the reasons provided in the last response. Specifically, it is well settled law that the term “about” is not indefinite *per se*. This standard was not applied in the instant situation, which appears to be based upon the view that “about 12” is indefinite in the absence of a definition (and thus *per se* indefinite).

However, and in light of the revisions to claims 1 and 8 to use “consisting of” as the transitional phrase, “about 12” is delimited by the maximum length of 13 as provided for by the literal scope of the claims. Applicants thus respectfully submit that there is no possibility of any confusion as to whether “about 12” would include “a 20, 25, 30, or 50 amino acid sequence”. Withdrawal of this rejection is thus respectfully requested.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7-10, 13, 14, 46, and 47 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to “reasonably provide enablement for any peptide ‘comprising’” the sequences recited in claims 1, 8 and 46.

As an initial matter, Applicants respectfully submit that no issue of non-enablement exists in light of the claim revisions provided above, which exclude the use of “comprising” and include the statement that the peptides bind  $\alpha 3 \beta 1$  integrin. Accordingly, Applicants believe that no *prima facie* case of undue experimentation exists, especially in light of the standard set out in part at MPEP 2164.04, including *In re Marzocchi*<sup>1</sup> and the other cases cited therein.

Once again, Applicants point out that no objective reason has been provided to question that undue experimentation is needed to make and use the claimed peptides, which are now of defined lengths, as encompassed by the revised claims.

To the contrary, the instant invention is similar to the situation seen with a common integrin binding motif, Arg-Gly-Asp (RGD) as discovered via fibronectin. In the case

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<sup>1</sup> 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

of the RGD sequence, there is no reason to doubt that it is possible to make and use a variety of peptides containing the sequence, which retain the ability to bind integrin, without undue experimentation. This follows because while there may be some unpredictability as to whether some peptides having the RGD sequence will misfold as to present a structure that will not bind integrin, the amount of experimentation necessary to address this unpredictability is not undue.

The instant invention is directed to an analogous situation because no objective reasons have been provided as to why the instant tetrameric sequence, as recited in claims 1, 8, and 46, cannot be treated in the same manner as the RGD sequence known in the art. Both sequences are in the same, and more specific, field of integrin binding peptides. Accordingly, the reliance upon the articles by Kuntz et al. and Miller et al. (in the previous Office Action mailed May 21, 2004) is misplaced because the content of both fail to take either the RGD sequence or the instant tetrameric sequence into consideration. Instead, the content of both paint a picture of the situations with other proteins and polypeptides that are unrelated to the peptides of the invention. Accordingly, Applicants respectfully submit that the contents of those references are not dispositive relative to the instant application.

A much more relevant comparison to the instant application is present in *In re Wands*<sup>2</sup> (copy attached), where no undue experimentation was present to support an assertion of a lack of enablement. The facts of *Wands* involve claims directed to immunoassays to detect hepatitis B surface antigen (HBsAg) by use of monoclonal antibodies (MAb) which bind the antigen, wherein the MAb have a high affinity of at least  $10^{-9}$  M for the antigen. The claims were solely rejected as requiring undue experimentation to make the MAb needed to practice the invention. The Patent and Trademark Office (PTO) took the position that “data presented by *Wands* show that the production of high affinity IgM anti-HBsAg antibodies is unpredictable and unreliable.”<sup>3</sup> There was no issue of “how to use” the *Wands* invention because, like in the instant application where one skilled in the art would know how to use the peptides to bind  $\alpha 3\beta 1$

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<sup>2</sup> 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

<sup>3</sup> *Id.* at 1402.

integrin as disclosed, one skilled in the art would know how to use the high affinity MAb in the claimed immunoassays.

The Federal Circuit accepted the Wands argument that “methods to make high-affinity IgM anti-HBsAg antibodies requires only routine screening, and that does not amount to undue experimentation.”<sup>4</sup> More specifically, the Federal Circuit stated clearly that “[e]nablement is not precluded by the necessity for some experimentation such as routine screening.”<sup>5</sup> The court then continued by reviewing the process for producing monoclonal antibodies by use of hybridoma cells followed by the following:

The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which one secrete antibodies with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.... Furthermore, in the monoclonal antibody art it appears that an ‘experiment’ is not simply the screening of a single hybridoma but is rather the entire attempt to make a monoclonal antibody against a particular antigen.... Wands carried out this entire procedure [to make a monoclonal antibody] three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations.<sup>6</sup>

The Federal Circuit then proceeded to conclude that no undue experimentation was needed to obtain antibodies to practice the claimed invention.

The facts and law in *Wands* are directly applicable to the instant invention because like MAb, the claimed peptides are polypeptides that bind a target molecule (HBsAg in *Wands* and  $\alpha 3\beta 1$  integrin in the instant invention). The situations are also similar in the sense that like the MAb situation, the claimed peptides are not prepared by an “experiment” that is simply the screening of a single peptide. To the contrary, the instant peptides can be prepared in

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<sup>4</sup> *Id.* at 1404.

<sup>5</sup> *Id.*

<sup>6</sup> *Id.* at 1406-7.

combinations such that multiple peptides are prepared and screened simultaneously where the skilled artisan is prepared to screen “negative” peptides that do not have  $\alpha 3 \beta 1$  integrin binding activity.

This latter parallel between *Wands* and the instant application is demonstrated not only by the peptides shown on page 34, Table 2, of the application, but also by the results of alanine scanning across the binding sequence as shown on page 36, Table 3. Table 3 shows that substitution of an alanine (alanine scanning mutagenesis) for 9 of 12 positions<sup>7</sup> in a dodecameric peptide containing the NVRF tetrameric sequence, the binding affinity is unchanged for positions outside the tetrameric NVFR core motif. Accordingly, one skilled in the art presented with these results would expect that the majority, if not all, of positions outside the tetrameric core motif may be substituted with other amino acid residues without deleterious effects on binding to  $\alpha 3 \beta 1$  integrin. *The instant statement of the rejection provides no objective reason to counter this view.* Moreover, and because the facts of *Wands* are so much more applicable to the instant application, no reliance on *In re Fisher* is acceptable where it differs from the situation in *Wands* and the instant invention.

Therefore, and to the extent that any residual concern may be present with respect to enablement for the revised claims based upon a possible need for screening assays or the definitions of the R<sub>1</sub> and R<sub>2</sub> groups in the claims, Applicants respectfully submit that as previously explained, no more than routine and repetitive experimentation, like that in *Wands*, is needed to make and use the instantly claimed invention.

This position is also applicable to claims 13 and 14 (as well as new claims 51-52) because contrary to the statement of the rejection, the instant application describes the use of peptides to inhibit vascularization in a chick chorioallantoic membrane, or CAM, (see pages 47-48, Table 5) as well as modulate endothelial cell and SCLC proliferation and other behavior (see pages 40-46). The correlation between a CAM assay and angiogenesis is well known such that the former is used as a screen to increase the expectation of successfully using a molecule to

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<sup>7</sup> The three unsubstituted positions are those occupied by Gly (third residue), Val (fourth residue), and Val (eleventh residue), which are already small side chain residues like alanine.

inhibit the latter. Similarly, the correlation between inhibition of cell proliferation in vitro and in vivo provides a reasonable basis to support the claims as filed.

Given the guidance provided by the instant application and the absence of objective reasons to doubt the presence of an enabling disclosure given the disclosure as provided, the claimed invention must be **presumed enabled**. Accordingly, Applicants respectfully request withdrawal of the instant rejection.

Claims 1-5, 7-10, 13, 14, 46 and 47 were rejected under 35 U.S.C. § 112, first paragraph as allegedly “failing to comply with the written description requirement.” Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of an inadequate written description has been presented.

As an initial matter, Applicants point out that the statement of the rejection asserts that

there is no described or art-recognized correlation or relationship between the structure of the invention, the generic formulae and its anti-angiogenic, anti-proliferation function (i.e., inhibition of a  $\alpha 3\beta 1$ /TSP interaction), the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of variants which retain the features essential to the instant rejection. (see page 6 of the previous Office Action)

Applicants respectfully submit that contrary to the position reflected by the above quote, the instant application clearly asserts that the disclosed tetrameric core motif is responsible for (or correlated with) the activities of the invention as disclosed. Moreover, Applicants strongly disagree with the apparent assertion that the correlation needs to be “art-recognized”. How can this be the standard? Is it not possible for an application, like the instant one, to disclose a correlation between structure and function for the first time? Applicants respectfully submit that this possibility must be available and so the view taken in the instant rejection cannot stand.

Additionally, the above quote seems to admit that the instant application discloses at least anti-angiogenic and anti-proliferative uses of the claimed invention in relationship to  $\alpha 3 \beta 1$  integrin binding. This is at odds with the rejection addressed above, which asserted that no such properties were available for the use of the compositions of claims 13 and 14 (as well as claims 51 and 52).

To the extent that this rejection is based upon the view that amino acid residues in the R<sub>1</sub> and R<sub>2</sub> groups must be defined to provide a written description, Applicants strongly disagree because the invention is based upon the tetrameric core motif as claimed. This is supported by the data on page 36, Table 3. Applicants believe that it is improper for the Office to redefine the invention to be something other than that which Applicants claim.

In light of the above, as well as the **strong presumption** of an adequate written description as discussed in the previous response, Applicants simply do not believe that any issue of an inadequate written description is present. Accordingly, withdrawal of this rejection is respectfully requested.

Claim 46 was also rejected under 35 U.S.C. § 112, first paragraph as allegedly containing "new matter." As noted above, Applicants understand that this rejection has been obviated based upon the discussion during the telephonic interview, where support for claim 46 as found in original claim 1 was sufficient.

Applicants respectfully request an indication of this rejection has having been withdrawn.

#### Claim Rejections under 35 U.S.C. § 102

Claims 1-2, 5, and 13-14 were rejected under 35 U.S.C. § 102(a) as allegedly anticipated by JP10-25896 (9/1998). This was discussed during the telephonic interview where the actual teachings of the cited reference were unclear in the absence of a translation of the relative portions of the document. For example, it is unclear whether the sequence in the reference as relied upon is merely a portion of a larger sequence.



While Examiner Haddad will endeavor to obtain a translation of the cited reference, Applicants point out that this rejection is not applicable to the revised claims, which no longer recite “comprising”. Accordingly, this rejection may be properly withdrawn.

Claims 1-2 and 5 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Fowlkes et al. (USP 5,789,184).

Applicants have carefully reviewed the statement of the instant rejection and respectfully point out that the reference fails to actual disclose a peptide. Fowlkes et al. only describe the isolation of plasmids containing particular sequences that are manually interpreted as encoding the sequence of SEQ ID NO:55 in the reference (see column 61, lines 40-59). This is not a disclosure of an actual peptide having that sequence because no such peptide is taught to exist. Applicants respectfully submit that it is entirely possible that the peptide is not expressed or is expressed as a larger or truncated version. Simply put, it is not clear whether a peptide having only SEQ ID NO:55 is actually in existence based on the cited reference. Accordingly, no *prima facie* case of anticipation has been presented.

Moreover, Applicants point out that this rejection is not applicable to the revised claims, which no longer recite “comprising”. This presents a second reason why no *prima facie* case is present. Accordingly, this rejection may be properly withdrawn for both of these reasons.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 7-9 and 13-14 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over either of JP10-25896 or Fowlkes et al. in view of USP 5,770,563 (Roberts et al.).

Applicants have carefully reviewed the statement of the instant rejection and respectfully submit that no *prima facie* case of obviousness has been presented. As noted above, neither of JP10-25896 and Fowlkes et al. is properly applicable to the claims from which claims 7-9 and 13-14 depend. Accordingly, this rejection may be withdrawn for this reason.

Additionally, Applicants respectfully point out that no adequate reason or motivation has been provided for why an ordinary artisan would combine the references as alleged. The teachings of JP10-25896 are unclear for the reasons provided above. Given no knowledge as to that disclosure, why would one of ordinary skill combine it with the thrombospondin peptides of Roberts et al.? The simple answer is that they would not in the absence of impermissible hindsight reconstruction.

Similarly, why would the ordinary artisan combine the teachings of Fowlkes et al., which relate to yeast pheromone technology, combine them with the thrombospondin peptides of Roberts et al.? Again, there would be no suggestion or motivation without use of impermissible hindsight based on the instant application.

In addition to these reasons, Applicants point out that this rejection is not applicable to the revised claims, which no longer recite "comprising". Accordingly, this rejection may be properly withdrawn for all of these reasons.

### CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6100.

Respectfully submitted,



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**FULL TEXT OF CASES (USPQ2D)**

All Other Cases

**In re Wands (CA FC) 8 USPQ2d 1400 In re Wands****U.S. Court of Appeals Federal Circuit  
8 USPQ2d 1400****Decided September 30, 1988  
No. 87-1454****Headnotes****PATENTS****1. Patentability/Validity -- Adequacy of disclosure (§ 115.12)**

Data disclosed in application for immunoassay method patent, which shows that applicants screened nine of 143 cell lines developed for production of antibody necessary to practice invention, stored remainder of said cell lines, and found that four out of nine cell lines screened produced antibody falling within limitation of claims, were erroneously interpreted by Board of Patent Appeals and Interferences as failing to meet disclosure requirements of 35 USC 112, since board's characterization of stored cell lines as "failures" demonstrating unreliability of applicants' methods was improper in view of fact that such unscreened cell lines prove nothing concerning probability of success of person skilled in art attempting to obtain requisite antibodies using applicants' methods.

**2. Patentability/Validity -- Adequacy of disclosure (§ 115.12)**

Disclosure in application for immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring "undue experimentation," even though production of monoclonal antibodies necessary to practice invention first requires production and screening of numerous antibody producing cells or "hybridomas," since practitioners of art are prepared to screen negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art one "experiment" is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired

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antibodies is not excessive, in view of applicants' success in each attempt to produce antibody that satisfied all claim limitations.

## **Case History and Disposition:**

Page 1400

**Appeal from decision of Patent and Trademark Office, Board of Patent Appeals and Interferences.**

**Application for patent of Jack R. Wands, Vincent R. Zurawski, Jr., and Hubert J. P. Schoemaker, serial number 188,735. From decision of Board of Patent Appeals and Interferences affirming rejection of application, applicants appeal. Reversed; Newman, J., concurring in part and dissenting in part in separate opinion.**

### **Attorneys:**

**Jorge A. Goldstein, of Saidman, Sterne, Kessler & Goldstein (Henry N. Wixon, with them on brief), Washington, D.C., for appellant.**

**John H. Raubitschek, associate solicitor (Joseph F. Nakamura and Fred E. McKelvey, with him on brief), PTO, for appellee.**

### **Judge:**

**Before Smith, Newman, and Bissell, circuit judges.**

## **Opinion Text**

### **Opinion By:**

**Smith, J.**

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (board) affirming the rejection of all remaining claims in appellant's application for a patent, serial No. 188,735, entitled "Immunoassay Utilizing Monoclonal High Affinity IgM

Page 1401

Antibodies," which was filed September 19, 1980. 1 The rejection under 35 U.S.C. §112, first paragraph, is based on the grounds that appellant's written specification would not enable a person skilled in the art to make the monoclonal antibodies that are needed to practice the claimed invention without undue experimentation. We

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reverse.

## I. Issue

The only issue on appeal is whether the board erred, as a matter of law, by sustaining the examiner's rejection for lack of enablement under 35 U.S.C. §112, first paragraph, of all remaining claims in appellants' patent application, serial No. 188,735.

## II. Background

### A. The Art .

The claimed invention involves immunoassay methods for the detection of hepatitis B surface antigen by using high-affinity monoclonal antibodies of the IgM isotype. *Antibodies* are a class of proteins (immunoglobulins) that help defend the body against invaders such as viruses and bacteria. An antibody has the potential to bind tightly to another molecule, which molecule is called an antigen. The body has the ability to make millions of different antibodies that bind to different antigens. However, it is only after exposure of an antigen that a complicated *immune response* leads to the production of antibodies against that antigen. For example, on the surface of hepatitis B virus particles there is a large protein called *hepatitis B surface antigen* (HBsAg). As its name implies, it is capable of serving as an antigen. During a hepatitis B infection (or when purified HBsAg is injected experimentally), the body begins to make antibodies that bind tightly and specifically to HBsAg. Such antibodies can be used as reagents for sensitive diagnostic tests ( *e.g.* , to detect hepatitis B virus in blood and other tissues, a purpose of the claimed invention). A method for detecting or measuring antigens by using antibodies as reagents is called an *immunoassay* .

Normally, many different antibodies are produced against each antigen. One reason for this diversity is that different antibodies are produced that bind to different regions (determinants) of a large antigen molecule such as HBsAg. In addition, different antibodies may be produced that bind to the same determinant. These usually differ in the tightness with which they bind to the determinant. *Affinity* is a quantitative measure of the strength of antibody-antigen binding. Usually an antibody with a higher affinity for an antigen will be more useful for immunological diagnostic tests than one with a lower affinity. Another source of heterogeneity is that there are several immunoglobulin classes or *isotypes* . Immunoglobulin G (IgG) is the most common isotype in serum. Another isotype, immunoglobulin M (IgM), is prominent early in the immune response. IgM molecules are larger than IgG molecules, and have 10 antigen-binding sites instead of the 2 that are present in IgG. Most immunoassay methods use IgG, but the claimed invention uses only IgM antibodies.

For commercial applications there are many disadvantages to using antibodies from serum. Serum contains a complex mixture of antibodies against the antigen of interest within a much larger pool of antibodies directed at other antigens. There are available only in a limited supply that ends when the donor dies. The goal of monoclonal antibody technology is to produce an unlimited supply of a single purified antibody.

The blood cells that make antibodies are *lymphocytes* . Each lymphocyte makes only one kind of antibody. During an immune response, lymphocytes exposed to their particular antigen divide and mature. Each produces a *clone* of identical daughter cells, all of which secrete the same antibody. Clones of lymphocytes, all derived from a single lymphocyte, could provide a source of a single homogeneous antibody. However, lymphocytes do not survive for long outside of the body in cell culture.

Hybridoma technology provides a way to obtain large numbers of cells that all produce the same antibody. This method takes advantage of the properties of *myeloma* cells derived from a tumor of the immune system. The cancerous myeloma cells can divide indefinitely in vitro. They also have the potential ability to secrete antibodies. By appropriate experimental manipulations, a myeloma cell can be made to fuse with a lymphocyte to produce a single hybrid cell (hence, a hybridoma) that contains the genetic material of both cells. The hybridoma secretes the same antibody that was made by its parent lymphocyte, but acquires the capability of the myeloma cell to divide

and grow indefinitely in cell culture. Antibodies produced by a clone of hybridoma cells (i.e., by hybridoma

Page 1402

cells that are all progeny of a single cell) are called monoclonal antibodies. 2

## **B. The Claimed Invention .**

The claimed invention involves methods for the immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. Jack R. Wands and Vincent R. Zurawski, Jr., two of the three coinventors of the present application, disclosed methods for producing monoclonal antibodies against HBsAg in United States patent No. 4,271,145 (the '145 patent), entitled "Process for Producing Antibodies to Hepatitis Virus and Cell Lines Therefor," which patent issued on June 2, 1981. The '145 patent is incorporated by reference into the application on appeal. The specification of the '145 patent teaches a procedure for immunizing mice against HBsAg, and the use of lymphocytes from these mice to produce hybridomas that secrete monoclonal antibodies specific for HBsAg. The '145 patent discloses that this procedure yields both IgG and IgM antibodies with high-affinity binding to HBsAg. For the stated purpose of complying with the best mode requirement of 35 U.S.C. §112, first paragraph, a hybridoma cell line that secretes IgM antibodies against HBsAg (the 1F8 cell line) was deposited at the American Type Culture Collection, a recognized cell depository, and became available to the public when the '145 patent issued.

The application on appeal claims methods for immunoassay of HBsAg using monoclonal antibodies such as those described in the '145 patent. Most immunoassay methods have used monoclonal antibodies of the IgG isotype. IgM antibodies were disfavored in the prior art because of their sensitivity to reducing agents and their tendency to self-aggregate and precipitate. Appellants found that their monoclonal IgM antibodies could be used for immunoassay of HbsAg with unexpectedly high sensitivity and specificity. Claims 1, 3, 7, 8, 14, and 15 are drawn to methods for the immunoassay of HBsAg using high-affinity IgM monoclonal antibodies. Claims 19 and 25-27 are for chemically modified ( *e.g.* , radioactively labeled) monoclonal IgM antibodies used in the assays. The broadest method claim reads:

1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:

contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and determining the presence of said substance in said sample;

wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least  $10^9 M^{-1}$ .

Certain claims were rejected under 35 U.S.C. §103; these rejections have not been appealed. Remaining claims 1, 3, 7, 8, 14, 15, 19, and 25-27 were rejected under 35 U.S.C. §112, first paragraph, on the grounds that the disclosure would not enable a person skilled in the art to make and use the invention without undue experimentation. The rejection is directed solely to whether the specification enables one skilled in the art to make the monoclonal antibodies that are needed to practice the invention. The position of the PTO is that data presented by Wands show that the production of high-affinity IgM anti-HBsAg antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.

## **III. Analysis**

### **A. Enablement by Deposit of Micro-organisms and Cell Lines .**

The first paragraph of 35 U.S.C. §112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention. "Patents \* \* \* are written to enable those skilled in the art to practice the invention." 3 A patent need not disclose what is well known in the art. 4 Although we review underlying facts

found by the board under a "clearly erroneous" standard, 5 we review enablement as a question of law. 6 Where an invention depends on the use of living materials such as microorganisms or

Page 1403

cultured cells, it may be impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure. One means that has been developed for complying with the enablement requirement is to deposit the living materials in cell depositories which will distribute samples to the public who wish to practice the invention after the patent issues. 7 Administrative guidelines and judicial decisions have clarified the conditions under which a deposit of organisms can satisfy the requirements of section 112. 8 A deposit has been held necessary for enablement where the starting materials (i.e., the living cells used to practice the invention, or cells from which the required cells can be produced) are not readily available to the public. 9 Even when starting materials are available, a deposit has been necessary where it would require undue experimentation to make the cells of the invention from the starting materials. 10

In addition to satisfying the enablement requirement, deposit of organisms also can be used to establish the filing date of the application as the *prima facie* date of invention, 11 and to satisfy the requirement under 35 U.S.C. §114 that the PTO be guaranteed access to the invention during pendency of the application. 12 Although a deposit may serve these purposes, we recognized, in *In re Lundak*, 13 that these purposes, nevertheless, may be met in ways other than by making a deposit.

A deposit also may satisfy the best mode requirement of section 112, first paragraph, and it is for this reason that the 1F8 hybridoma was deposited in connection with the '145 patent and the current application. Wands does not challenge the statements by the examiner to the effect that, although the deposited 1F8 line enables the public to perform immunoassays with antibodies produced by that single hybridoma, the deposit does not enable the generic claims that are on appeal. The examiner rejected the claims on the grounds that the written disclosure was not enabling and that the deposit was inadequate. Since we hold that the written disclosure fully enables the claimed invention, we need not reach the question of the adequacy of deposits.

## **B. Undue Experimentation .**

Although inventions involving microorganisms or other living cells often can be enabled by a deposit, 14 a deposit is not always necessary to satisfy the enablement requirement. 15 No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation. 16 Whether the specification in an application involving living cells (here, hybridomas) is enabled without a deposit must be decided on the facts of the particular case. 17

Appellants contend that their written specification fully enables the practice of

Page 1404

their claimed invention because the monoclonal antibodies needed to perform the immunoassays can be made from readily available starting materials using methods that are well known in the monoclonal antibody art. Wands states that application of these methods to make high-affinity IgM anti-HBsAg antibodies requires only routine screening, and that does not amount to undue experimentation. There is no challenge to their contention that the starting materials (i.e., mice, HBsAg antigen, and myeloma cells) are available to the public. The PTO concedes that the methods used to prepare hybridomas and to screen them for high-affinity IgM antibodies against HBsAg were either well known in the monoclonal antibody art or adequately disclosed in the '145 patent and in the current application. This is consistent with this court's recognition with respect to another patent application that methods for obtaining and screening monoclonal antibodies were well known in 1980. 18 The sole issue is whether, in this

particular case, it would require undue experimentation to produce high-affinity IgM monoclonal antibodies. Enablement is not precluded by the necessity for some experimentation such as routine screening. 19 However, experimentation needed to practice the invention must not be undue experimentation. 20 "the key word is 'undue,' not 'experimentation.'" 21

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* [448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 1971), *cert. denied*, 404 U.S. 1018 [ 172 USPQ 257 ] (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed \* \* \* . 22

The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. 23 Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. The board concluded that undue experimentation would be needed to practice the invention on the basis of experimental data presented by Wands. These data are not in dispute. However, Wands and the board disagree strongly on the conclusion that should be drawn from that data. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* . 24 They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. 25

In order to understand whether the rejection was proper, it is necessary to discuss further the methods for making specific monoclonal antibodies. The first step for making monoclonal antibodies is to immunize an animal. The '145 patent provides a detailed description of procedures for immunizing a specific strain of mice against HBsAg. Next the spleen, an organ rich in lymphocytes, is removed and the lymphocytes are separated from the other spleen cells. The lymphocytes are mixed with myeloma cells, and the mixture is treated to cause a few of the cells to fuse with each other. Hybridoma cells that secrete the desired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening procedures.

The first step is to separate the hybridoma cells from unfused lymphocytes and myeloma cells. The cells are cultured in a medi

Page 1405

um in which all the lymphocytes and myeloma cells die, and only the hybridoma cells survive. The next step is to isolate and clone hybridomas that make antibodies that bind to the antigen of interest. Single hybridoma cells are placed in separate chambers and are allowed to grow and divide. After there are enough cells in the clone to produce sufficient quantities of antibody to analyze, the antibody is assayed to determine whether it binds to the antigen. Generally, antibodies from many clones do not bind the antigen, and these clones are discarded. However, by screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest.

Wands used a commercially available radioimmunoassay kit to screen clones for cells that produce antibodies directed against HBsAg. In this assay the amount of radioactivity bound gives some indication of the strength of the antibody-antigen binding, but does not yield a numerical affinity constant, which must be measured using the more laborious Scatchard analysis. In order to determine which anti-HBsAg antibodies satisfy all of the limitations of appellants' claims, the antibodies require further screening to select those which have an IgM isotype and have a binding affinity constant of at least  $10^9 \text{M}^{-1}$ . 26 The PTO does not question that the screening techniques used by Wands were well known in the monoclonal antibody art.

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During prosecution Wands submitted a declaration under 37 C.F.R. §1.132 providing information about all of the hybridomas that appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas. The next six fusion experiments all produced hybridomas that made antibodies specific for HBsAg. Antibodies that bound at least 10,000 cpm in the commercial radioimmunoassay were classified as "high binders." Using this criterion, 143 high-binding hybridomas were obtained. In the declaration, Wands stated that 27

It is generally accepted in the art that, among those antibodies which are binders with 50,000 cpm or higher, there is a very high likelihood that high affinity ( $K_a$  [greater than]  $10^9 M^{-1}$ ) antibodies will be found. However, high affinity antibodies can also be found among high binders of between 10,000 and 50,000, as is clearly demonstrated in the Table.

The PTO has not challenged this statement.

The declaration stated that a few of the high-binding monoclonal antibodies from two fusions were chosen for further screening. The remainder of the antibodies and the hybridomas that produced them were saved by freezing. Only nine antibodies were subjected to further analysis. Four (three from one fusion and one from another fusion) fell within the claims, that is, were IgM antibodies and had a binding affinity constant of at least  $10^9 M^{-1}$ . Of the remaining five antibodies, three were found to be IgG, while the other two were IgM for which the affinity constants were not measured (although both showed binding well above 50,000 cpm).

Apparently none of the frozen cell lines received any further analysis. The declaration explains that after useful high-affinity IgM monoclonal antibodies to HBsAg had been found, it was considered unnecessary to return to the stored antibodies to screen for more IgMs. Wands says that the existence of the stored hybridomas was disclosed to the PTO to comply with the requirement under 37 C.F.R. §1.56 that applicants fully disclose all of their relevant data, and not just favorable results. 28 How these stored hybridomas are viewed is central to the positions of the parties.

The position of the board emphasizes the fact that since the stored cell lines were not completely tested, there is no proof that any of them are IgM antibodies with a binding affinity constant of at least  $10^9 M^{-1}$ . Thus, only 4 out of 143 hybridomas, or 2.8 percent, were *proved* to fall within the claims. Furthermore, antibodies that were proved to be high-affinity IgM came from only 2 of 10 fusion experiments. These statistics are viewed by the board as evidence that appellants' methods were not predictable or reproducible. The board concludes that Wands' low rate of demonstrated success shows that a person skilled in the art would have to

Page 1406

engage in undue experimentation in order to make antibodies that fall within the claims.

Wands views the data quite differently. Only nine hybridomas were actually analyzed beyond the initial screening for HBsAg binding. Of these, four produced antibodies that fell within the claims, a respectable 44 percent rate of success. (Furthermore, since the two additional IgM antibodies for which the affinity constants were never measured showed binding in excess of 50,000 cpm, it is likely that these also fall within the claims.) Wands argues that the remaining 134 unanalyzed, stored cell lines should not be written off as failures. Instead, if anything, they represent partial success. Each of the stored hybridomas had been shown to produce a high-binding antibody specific for HBsAg. Many of these antibodies showed binding above 50,000 cpm and are thus highly likely to have a binding affinity constant of at least  $10^9 M^{-1}$ . Extrapolating from the nine hybridomas that were screened for isotype (and from what is well known in the monoclonal antibody art about isotype frequency), it is reasonable to assume that the stored cells include some that produce IgM. Thus, if the 134 incompletely analyzed cell lines are considered at all, they provide some support (albeit without rigorous proof) to the view that hybridomas falling within the claims are not so rare that undue experimentation would be needed to make them. The first four fusion attempts were failures, while high-binding antibodies were produced in the next six fusions.

Appellants contend that the initial failures occurred because they had not yet learned to fuse cells successfully. Once they became skilled in the art, they invariably obtained numerous hybridomas that made high-binding antibodies against HBsAg and, in each fusion where they determined isotype and binding affinity they obtained hybridomas that fell within the claims.

Wands also submitted a second declaration under 37 C.F.R. §1.132 stating that after the patent application was submitted they performed an eleventh fusion experiment and obtained another hybridoma that made a high-affinity IgM anti-HBsAg antibody. No information was provided about the number of clones screened in that experiment. The board determined that, because there was no indication as to the number of hybridomas screened, this declaration had very little value. While we agree that it would have been preferable if Wands had included this information, the declaration does show that when appellants repeated their procedures they again obtained a hybridoma that produced an antibody that fit all of the limitations of their claims.

[1] We conclude that the board's interpretation of the data is erroneous. It is strained and unduly harsh to classify the stored cell lines (each of which was proved to make high-binding antibodies against HBsAg) as failures demonstrating that Wands' methods are unpredictable or unreliable. 29 At worst, they prove nothing at all about the probability of success, and merely show that appellants were prudent in not discarding cells that might someday prove useful. At best, they show that high-binding antibodies, the starting materials for IgM screening and Scatchard analysis, can be produced in large numbers. The PTO's position leads to the absurd conclusion that the more hybridomas an applicant makes and saves without testing the less predictable the applicant's results become. Furthermore, Wands' explanation that the first four attempts at cell fusion failed only because they had not yet learned to perform fusions properly is reasonable in view of the fact that the next six fusions were all successful. The record indicates that cell fusion is a technique that is well known to those of ordinary skill in the monoclonal antibody art, and there has been no claim that the fusion step should be more difficult or unreliable where the antigen is HBsAg than it would be for other antigens.

[2] When Wands' data is interpreted in a reasonable manner, analysis considering the factors enumerated in *Ex parte Forman* leads to the conclusion that undue experimentation would not be required to practice the invention. Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that un

Page 1407

due experimentation would be defined in terms of the number of hybridomas that were never screened. Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics. Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations. Reasonably interpreted, Wands' record indicates that, in the production of high-affinity IgM antibodies against HBsAG, the amount of effort needed to obtain such antibodies is not excessive. Wands' evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure. 30

#### IV. Conclusion

Considering all of the factors, we conclude that it would not require undue experimentation to obtain antibodies needed to practice the claimed invention. Accordingly, the rejection of Wands' claims for lack of enablement under 35 U.S.C. §112, first paragraph, is reversed.

## REVERSED

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### Footnotes

Footnote 1. *In re Wands*, Appeal No. 673-76 (Bd. Pat. App. & Int. Dec. 30, 1986).

Footnote 2. For a concise description of monoclonal antibodies and their use in immunoassay see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1368-71, 231 USPQ 81, 82-83 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987).

Footnote 3. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Footnote 4. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Footnote 5. *Coleman v. Dines*, 754 F.2d 353, 356, 224 USPQ 857, 859 (Fed. Cir. 1985).

Footnote 6. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 810 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 875 (1987); *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960 n.6, 220 USPQ 592, 599 n.6 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 [ 225 USPQ 232 ] (1984).

Footnote 7. *In re Argoudelis*, 434 F.2d 1390, 1392-93, 168 USPQ 99, 101-02 (CCPA 1970).

Footnote 8. *In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985); *Feldman v. Aunstrup*, 517 F.2d 1351, 186 USPQ 108 (CCPA 1975), *cert. denied*, 424 U.S. 912 [ 188 USPQ 720 ] (1976); Manual of Patent Examining Procedure (MPEP) 608.01 (p)(C) (5th ed. 1983, rev. 1987). See generally Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement*, 67 J. Pat. Trademark Off. Soc'y 569 (1985).

Footnote 9. *In re Jackson*, 217 USPQ 804, 807-08 (Bd. App. 1982) (strains of a newly discovered species of bacteria isolated from nature); *Feldman*, 517 F.2d 1351, 186 USPQ 108 (uncommon fungus isolated from nature); *In re Argoudelis*, 434 F.2d at 1392, 168 USPQ at 102 (novel strain of antibiotic-producing microorganism isolated from nature); *In re Kropp*, 143 USPQ 148, 152 (Bd. App. 1959) (newly discovered microorganism isolated from soil).

Footnote 10. *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (genetically engineered bacteria where the specification provided insufficient information about the amount of time and effort required); *In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (unique cell line produced from another cell line by mutagenesis).

Footnote 11. *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95-96; *In re Feldman*, 517 F.2d at 1355, 186 USPQ at 113; *In re Argoudelis*, 434 F.2d at 1394-96, 168 USPQ at 103-04 (Baldwin, J. concurring).

Footnote 12. *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95-96; *In re Feldman*, 517 F.2d at 1354, 186 USPQ at 112.

Footnote 13. *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95-96.

Footnote 14. *In re Argoudelis*, 434 F.2d at 1393, 168 USPQ at 102.

Footnote 15. *Tabuchi v. Nubel*, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977).

Footnote 16. *Id.* at 1186-87, 194 USPQ at 525; *Merck & Co. v. Chase Chem. Co.*, 273 F.Supp. 68, 77, 155 USPQ 139, 146 (D.N.J. 1967); *Guaranty Trust Co. v. Union Solvents Corp.*, 54 F.2d 400, 403-06, 12 USPQ 47, 50-53 (D. Del. 1931), *aff'd*, 61 F.2d 1041, 15 USPQ 237 (3d Cir. 1932), *cert. denied*, 288 U.S. 614 (1933); MPEP 608.01 (p)(C) ("No problem exists when the microorganisms used are known and readily available to the public.").

Footnote 17. *In re Jackson* , 217 USPQ at 807; *see In re Metcalfe* , 410 F.2d 1378, 1382, 161 USPQ 789, 792 (CCPA 1969).

Footnote 18. *Hybritech* , 802 F.2d at 1384, 231 USPQ at 94.

Footnote 19. *Id.*; *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984); *In re Angstadt* , 537 F.2d at 502-504, 190 USPQ at 218; *In re Geerdes* , 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); *Mineral Separation, Ltd. v. Hyde* , 242 U.S. 261, 270-71 (1916).

Footnote 20. *Hybritech* , 802 F.2d at 1384, 231 USPQ at 94; *W.L. Gore* , 721 F.2d at 1557, 220 USPQ at 316; *In re Colianni* , 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977) (Miller, J., concurring).

Footnote 21. *In re Angstadt* , 537 F.2d at 504, 190 USPQ at 219.

Footnote 22. *In re Jackson* , 217 USPQ at 807.

Footnote 23. *See Hybritech* , 802 F.2d at 1384, 231 USPQ at 94; *Atlas Powder* , 750 F.2d at 1576, 224 USPQ at 413.

Footnote 24. *Ex parte Forman* , 230 USPQ at 547.

Footnote 25. *Id.*; *see In re Colianni* , 561 F.2d at 224, 195 USPQ at 153 (Miller, J., concurring); *In re Rainer* , 347 F.2d 574, 577, 146 USPQ 218, 221 (CCPA 1965).

Footnote 26. The examiner, the board, and Wands all point out that, technically, the strength of antibody-HBsAg binding is measured as *avidity* , which takes into account multiple determinants on the HBsAg molecule, rather than affinity. Nevertheless, despite this correction, all parties then continued to use the term "affinity." We will use the terminology of the parties. Following the usage of the parties, we will also use the term "high-affinity" as essentially synonymous with "having a binding affinity constant of at least  $10^9\text{M}^{-1}$ ."

Footnote 27. A table in the declaration presented the binding data for antibodies from every cell line. Values ranged from 13,867 to 125,204 cpm, and a substantial proportion of the antibodies showed binding greater than 50,000 cpm. In confirmation of Dr. Wand's statement, two antibodies with binding less than 25,000 cpm were found to have affinity constants greater than  $10^9\text{M}^{-1}$ .

Footnote 28. *See Rohm & Haas Co. v. Crystal Chem. Co.* , 722 F.2d 1556, 220 USPQ 98 (Fed. Cir. 1983).

Footnote 29. Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff.

Footnote 30. *In re Strahilevitz* , 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982).

### Concurring/Dissenting Opinion Text

#### Concurrence/Dissent By:

Newman, J., concurring in part, dissenting in part.

#### A

I concur in the court's holding that additional samples of hybridoma cell lines that produce these high-affinity IgM monoclonal antibodies need not be deposited. This invention, as described by Wands, is not a selection of a few rare cells from many possible cells. To the contrary, Wands states that all monoclonally produced IgM antibodies to hepatitis B surface antigen have the desired high avidity and other favorable properties, and that all are readily preparable by now-standard techniques.

Wands states that his United States Patent No. 4,271,145 describes fully operable techniques, and is distinguished from his first four failed experiments that are referred to in the Rule 132 affidavit. Wands argues that these biotechnological mechanisms are relatively well understood and that the preparations can be routinely duplicated by those of skill in this art, as in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* , 802 F.2d 1367, 1380, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied* , 107 S.Ct. 1606 (1987). I agree that it is not necessary that there be a

deposit of multiple exemplars of a cell system that is readily reproduced by known, specifically identified techniques.

## B

I would affirm the board's holding that Wands has not complied with 35 U.S.C. §112, first paragraph, in that he has not provided data sufficient to support the breadth of his generic claims. Wands' claims on appeal include the following:

19. Monoclonal high affinity IgM antibodies immunoreactive with HBsAg determinants, wherein said antibodies are coupled to an insoluble solid phase, and wherein the binding affinity constant of said antibodies for said HBsAg determinants is at least  $10^9 M^{-1}$ .

26. Monoclonal high affinity IgM antibodies immunoreactive with hepatitis B surface antigen.

Wands states that he obtained 143 "high binding monoclonal antibodies of the right specificity" in the successful fusions; although he does not state how they were determined to be high binding or of the right specificity, for Wands also states that only nine of these 143 were tested.

Of these nine, four (three from one fusion and one from another fusion) were found to have the claimed high affinity and to be of the IgM isotype. Wands states that the other five were either of a different isotype or their affinities were not determined. (This latter statement also appears to contradict his statement that all 143 were "high binding".)

Wands argues that a "success rate of four out of nine", or 44.4%, is sufficient to support claims to the entire class. The Commissioner deems the success rate to be four out of 143, or 2.8%; to which Wands responds with statistical analysis as to how unlikely it is that Wands selected the only four out of 143 that worked. Wands did not, however, prove the right point. The question is whether Wands, by testing nine out of 143 (the Commissioner points out that the randomness of the sample was not established), and finding that four out of the nine had the desired properties, has provided sufficient experimental support for the breadth of the requested claims, in the context that "experi

Page 1408

ments in genetic engineering produce, at best, unpredictable results", quoting from *Ex parte Forman*, 230 USPQ 546, 547 (Bd.Pat.App. and Int. 1986).

The premise of the patent system is that an inventor, having taught the world something it didn't know, is encouraged to make the product available for public and commercial benefit, by governmental grant of the right to exclude others from practice of that which the inventor has disclosed. The boundary defining the excludable subject matter must be carefully set: it must protect the inventor, so that commercial development is encouraged; but the claims must be commensurate with the inventor's contribution. Thus the specification and claims must meet the requirements of 35 U.S.C. §112. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 23-24 (CCPA 1970). As the science of biotechnology matures the need for special accommodation, such as the deposit of cell lines or microorganisms, may diminish; but there remains the body of law and practice on the need for sufficient disclosure, including experimental data when appropriate, that reasonably support the scope of the requested claims. That law relates to the sufficiency of the description of the claimed invention, and if not satisfied by deposit, must independently meet the requirements of Section 112.

Wands is not claiming a particular, specified IgM antibody. He is claiming all such monoclonal antibodies in assay for hepatitis B surface antigen, based on his teaching that such antibodies have uniformly reproducible high avidity, free of the known disadvantages of IgM antibodies such as tendency to precipitate or aggregate. It is incumbent upon Wands to provide reasonable support for the proposed breadth of his claims. I agree with the Commissioner that four exemplars shown to have the desired properties, out of the 143, do not provide adequate support.

Wands argues that the law should not be "harsher" where routine experiments take a long time. However, what Wands is requesting is that the law be less harsh. As illustrated in extensive precedent on the question of how much experimentation is "undue", each case must be determined on its own facts. See, e.g., *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976); *In re Cook*, 439 F.2d 730, 734-35, 169 USPQ 298, 302-03 (CCPA 1971).

The various criteria to be considered in determining whether undue experimentation is required are discussed in, for example, *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1971); *In re Rainer*, 347 F.2d 574, 146 USPQ 218 (CCPA 1965); *Ex parte Forman*, 230 USPQ at 547. Wands must provide sufficient data or authority to show that his results are reasonably predictable within the scope of the claimed generic invention, based on experiment and/or scientific theory. In my view he has not met this burden.

- End of Case -